PATENT SPECIFICATION (11) 1 330 966

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DRAWINGS ATTACHED

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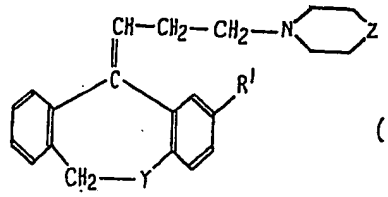
(54) N-SUBSTITUTED PIPERIDINE COMPOUNDS, METHODS FOR THEIR PRODUCTION, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

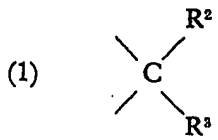
(71) We, YOSHITOMI PHARMACEUTICAL INDUSTRIES LTD., a Japanese Company, of No. 35 Hirano-Machi 3-Chome, Higashi-Ku, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel and therapeutically valuable N-substituted piperidine compounds of the formula:



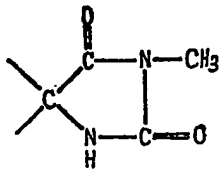
(I)

and pharmaceutically acceptable acid addition salts thereof, wherein Y is O, S or SO_2, R^1 is H, Cl, CH_3 or OCH_3 and Z is a bivalent group selected from groups of formulae:



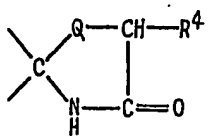
(1)

in which R^2 is OH, CN, $CONH_2$, CO_2H, or $COCH_3$ and R^3 is dimethylamino, piperidino, morpholino, phenyl, substituted phenyl (the substituent being Cl, CH_3 or CF_3) or acetylamino),



(2)

and



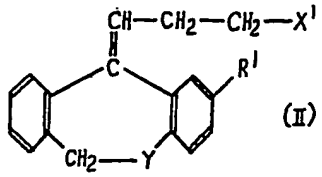
(3)

in which Q is O or S and R^4 is H, CH_3 or phenyl.

The compounds of formula (I) are produced by the following methods, wherein the symbols are as defined above except where otherwise stated:

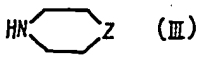
(a) By the reaction of a compound of the formula:

AP4



(II)

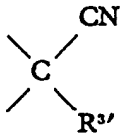
wherein X^1 is a reactive radical such as halogen, methylsulfonyloxy, phenylsulfonyloxy or tolylsulfonyloxy, with a compound of the formula:



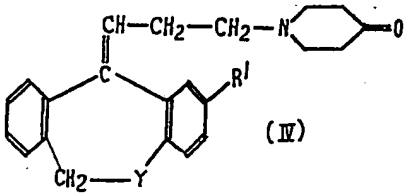
(III)

This reaction is usually carried out in a solvent, if necessary in the presence of a deacidifying agent and a condensation accelerator, usually at a temperature of 20° to 150°C. for a period of 5 to 10 hours. The solvent may be water, methanol, ethanol, acetone, dioxane, tetrahydrofuran, benzene, toluene, xylene, pyridine, dimethylformamide, dimethylsulfoxide or a mixed solvent thereof. The deacidifying agent may be sodium hydroxide, potassium hydroxide, sodium methoxide, potassium ethoxide, sodium carbonate, potassium carbonate, pyridine or triethylamine. The condensation accelerator may be an alkali metal iodide (e.g. NaI or KI).

(b) In order to produce the compounds of formula (I) wherein Z is



($R^{3'}$ being dimethylamino, piperidino or morpholino), by the reaction of a compound of the formula:



(IV)

with a cyanide of the formula

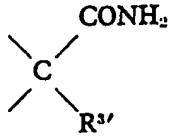
$$Me — CN \qquad (V)$$

wherein Me is hydrogen or an alkali metal, and with an amine of the formula

$$H — R^{3'} \qquad (VI)$$

This reaction is usually carried out in an inert solvent, such as water, an alcohol (e.g. methanol, ethanol or propanol), tetrahydrofuran, dioxane or a mixed solvent thereof, at a temperature from room temperature (e.g. 20°C.) to the boiling point of the solvent employed, for a period of 3 to 25 hours. Mostly, however, the reaction is carried out in a solvent, such as water, an alcohol or a mixed solvent thereof.

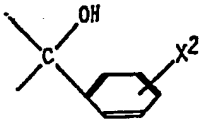
(c) In order to produce the compounds of formula (I) wherein Z is



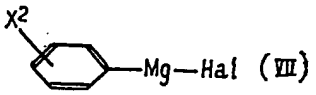
($R^{3'}$ being as defined above), by hydrolyzing a compound which is prepared by the method (b) mentioned above.

The hydrolysis may be, for example, carried out by adding 5 to 20 moles of 70 to 95 weight % per mole of the compound 95 weight % sulfuric acid per mole of the compound hydrolyzed, under heating at 60° to 95°C. for a period of 30 minutes to 3 hours.

(d) In order to produce the compounds of formula (I) wherein Z is



(X^2 being H, Cl, CH_3 or CF_3), by the reaction of a compound of formula (IV) above with a Grignard reagent of the formula



(VII)

wherein Hal is halogen.

The reaction may be carried out in the conventional way of carrying out a Grignard reaction, that is, by mixing a compound of formula (IV) and a compound of formula (VII), prepared from a phenyl or substituted phenyl halide and metallic magnesium, in an inert solvent such as diethyl ether, tetrahydrofuran, dioxane, diethylene glycol dimethyl ether or isopropyl ether, and then heating the resulting mixture at 20°C. to the boiling point of the solvent employed for 2 to 30 hours, and finally decomposing the reaction product with a dilute acid or aqueous ammonium chloride solution. It is possible to use, if necessary, another solvent, such as benzene, xylene, hexane or cyclohexane, as the inert solvent.

The starting compounds (II) and (IV) can be produced by, for example, the methods shown in the scheme which constitute the accompanying drawing. In the drawing, the symbol (i) refers to the method described in Canadian Patent Specification No. 717,977 and Chemical Abstracts, Vol. 64, 34436, and the symbol (ii) to the method described in J. Org. Chem., Vol. 27, page 4134 (1962).

The compounds of formula (I) can be converted into acid addition salts with various inorganic acids (e.g. hydrochloric, hydrobromic, sulfuric or nitric acid) or various organic acids (e.g. oxalic, maleic, fumaric, citric, tartaric or methanesulfonic acid).

The compounds of formula (I) and pharmaceutically acceptable acid addition salts thereof have excellent pharmacological actions, such as suppression of spontaneous motility and reserpine potentiation, as shown by the following tests.

The tests were carried out by the following procedures:

Suppression of Spontaneous Motility

Suppression of spontaneous motility was measured by the Photocell method described by P. B. Dews in "British Journal of Pharmacology" vol. 8, p. 46 ff. (1953). The procedure was as follows:

Each group consisting of five male mice (dd-strain mice weighing 20 to 25 g.) was kept in a compartment. Forty minutes after the intraperitoneal administration of the test compounds, the spontaneous motility was counted for 20 minutes. The ED_{50} shows the dose required for 50% suppression of spontaneous motility.

The results are shown in Table 1.

TABLE I

Compound	ED_{50} (mg./kg. body weight)
A	1.25 — 2.5
B	0.63 — 1.25
D	0.31 — 0.63
E	2.5 — 5.0
G	2.5 — 5.0

Reserpine Potentiation

Reserpine potentiation was measured by the method described by M. D. Aceto in "Toxicology and Applied Pharmacology" vol. 7, p. 329 ff. (1965). The procedure was as follows:

Thirty minutes after the oral administration of the test compounds to female mice (dd-strain mice weighing 20 to 25 g., each group consisting of four mice), reserpine (10 mg./kg. of body weight) was injected intraperitoneally. The degree of blepharoptosis of both eyes was observed 15, 60, 120 and 180 minutes after the administration of reserpine. The PD_{30} shows an effective dose potentiating the effect of reserpine by 30% 15 minutes after the administration of reserpine.

The results are shown in Table 2.

TABLE 2

Compound	PD_{30} (mg./kg. body weight)
A	0.63 — 1.25
B	0.31 — 0.63
C	1.25 — 2.5
E	0.63 — 1.25
F	0.31 — 1.25
G	0.31 — 0.63

In the above Tables, the test compounds (A, B, C, ..., G) are as follows:

A: 11 - [3 - (4 - carbamoyl - 4 - piperidinopiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin dihydrochloride 1/2 hydrate

B: 11 - [3 - (4 - hydroxy - 4 - phenylpiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin hydrochloride

C: 2 - chloro - 11 - [3 - (4 - carbamoyl-4 - piperidinopiperidino)propylidene] - 6,11-dihydrodibenz[b,e]oxepin dihydrochloride 1/2 hydrate

D: 11 - [3 - (4 - hydroxy - 4 - *p* - chlorophenylpiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin hydrochloride 1/2 hydrate

E: 11 - [3 - (4 - carbamoyl - 4 - morpholinopiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin dihydrochloride 1/2 hydrate

F: 11 - [3 - (2,4 - dioxo - 3 - methyl-1,3,8 - triazaspiro[4.5]dec - 8 - yl) propylidene] - 6,11 - dihydrodibenz[b,e]oxepin hydrocholride

G: 11 - [3 - (1 - thia - 3 - oxo - 4,8-diazaspiro[4.5]dec - 8 - yl)propylidene]-6,11 - dihydrodibenz[b,e]oxepin hydrochloride.

In view of the tests including those mentioned above, the compounds (I) of the present invention and pharmaceutically acceptable addition salts thereof can safely be administered orally as psychotropic agents for the treatment of schizophrenia, psychoneurosis, manic-depressive psychosis and the like disorders, in the form of a pharmaceutical preparation with a suitable and conventional pharmaceutically acceptable carrier or adjuvant. The invention also includes such preparations.

The oral daily dose of a compound (I) or a salt thereof for human adults is usually from 30 to 200 milligrams.

The pharmaceutical preparations can take any conventional form, such as tablets, capsules, powders or granules.

The following are examples of the preparations to be taken when the compounds (I) of the present invention and their acid addition salts are administered pharmaceutically.

(i) 5 mg. and 25 mg. tablets are prepared from the following compositions:

	5 mg. Tablet	25 mg. Tablet
Compound E	5 mg.	25 mg.
Lactose	62	64
Microcrystalline cellulose	10	15
Methyl cellulose	1	1
Starch	7	10
Talc	4	4
Magnesium stearate	1	1
	90 mg.	120 mg.

(ii) powders are prepared from the following composition:

Compound E	10%
Lactose	69
Starch	20
Methyl cellulose	1
Total	100%

The present invention will be better understood from the following Examples, which are illustrative of the present invention.

EXAMPLE 1.

A mixture of 7.5 g. of 11 - (3 - bromopropylidene) - 6,11 - dihydrodibenz[b,e]oxepin, 6 g. of 4 - carbamoyl - 4 - piperidinopiperidine, 4.9 g. of potassium carbonate, 30 ml. of toluene and 30 ml. of dimethylformamide is heated at 110°—120°C. with stirring for 6 hours. Then cold water is added to the reaction mixture, and the whole is extracted with toluene and washed with water. The toluene layer is extracted with dilute hydrochloric acid and the extract is made alkaline with potassium carbonate, with cooling. The

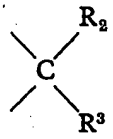
brown oil liberated is extracted with chloroform, the extract is dried and the chloroform is distilled off. The jelly-like residue is dissolved in ethanol, and hydrogen chloride gas is introduced into the solution. The crystals precipitated are collected and refined from aqueous ethanol to give 11 - [3 - (4 - carbamoyl - 4 - piperidino - piperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin dihydrochloride 1/2 hydrate, melting at 283°C. (decomposition).

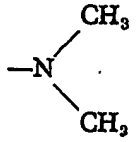
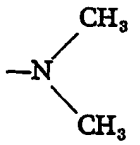
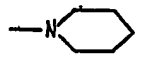
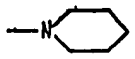
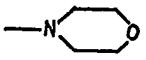
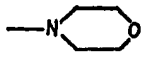
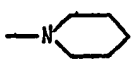
EXAMPLE 2.

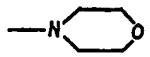
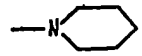
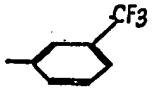
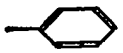
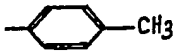
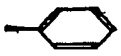
A mixture of 7 g. of 11 - (3 - bromopropylidene) - 6,11 - dihydrodibenz[b,e]oxepin, 5.1 g. of 4 - hydroxy - 4 - phenylpiperidine, 4.6 g. of potassium carbonate, 30 ml. of toluene and 30 ml. of dimethylformamide is heated at 110°—120°C. with stirring for 6 hours. After cooling, water is added to the reaction mixture, and the whole is extracted with toluene and washed with water. Then 20 ml. of 5% hydrochloric acid are added to the toluene layer. The jelly-like oil liberated is separated by decantation, and dissolved in chloroform. After drying, the chloroform is distilled off. The residue is dissolved in 30 ml. of acetone, and the solution is allowed to stand in a cold room to cause crystallization. The crystals obtained are refined from 2-propanol to give 11 - [3 - (4 - hydroxy - 4 - phenylpiperidino)-propylidene] - 6,11 - dihydrodibenz[b,e]-oxepin monohydrochloride, melting at 212°—213°C.

EXAMPLE 3 to 26.

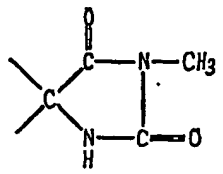
Other examples of compounds (I) and acid addition salts thereof which can be produced from a compound (II) and a compound (III) in a manner similar to that described in Example 1 or 2 are shown in the following Tables.

Examples of compounds (I) wherein Z is  are as follows

Example	Y	R^1	R^2	R^3	Salt and Melting Point (°C)
3	O	H	$-CONH_2$		2HCl 256—257 (decomposition)
4	O	$-CH_3$	$-CONH_2$		2HCl 1/2 H_2O 256 (decomposition)
5	O	—Cl	$-CONH_2$		2HCl 1/2 H_2O 280—281 (decomposition)
6	O	$-OCH_3$	$-CONH_2$		2HCl 269 (decomposition)
7	O	H	$-CONH_2$		2HCl 1/2 H_2O 255—256 (decomposition)
8	O	—Cl	$-CONH_2$		2HCl 1/2 H_2O 264 (decomposition)
9	S	H	$-CONH_2$		2HCl 274—275 (decomposition)

Example	Y	R^1	R^2	R^3	Salt and Melting Point (°C)
10	S	H	$-CONH_2$		2HCl 1/2 H_2O 261 (decomposition)
11	SO_2	H	$-CONH_2$		2HCl 1/2 H_2O 279—280 (decomposition)
12	O	H	—OH		HCl 1/2 H_2O 174—176
13	O	H	—OH		HCl 198—200
14	O	$-CH_3$	—OH		HCl 159
15	O	$-OCH_3$	—OH		HCl 156 (decomposition)
16	S	H	—OH		HCl 120
17	S	H	—OH		HCl 159—160
18	SO_2	H	—OH		HCl 105
19	O	H	—CN		HCl 245—247
20	O	H	$-COCH_3$		HCl 1/2 2-propanol 220—222
21	O	H	$-COOC_2H_5$	$-NHCOCH_3$	HCl 213—232 (decomposition)

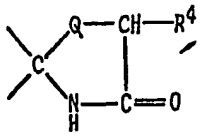
An example of a compound (I) wherein Z is



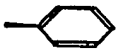
is as follows:

Example	Y	R_1	Salt and Melting point (°C.)
22	O	H	HCl 298 (decomposition)

Examples of compounds (I) wherein Z is



are as follows:

Example	Y	R^1	Q	R^4	Salt and Melting Point (°C)
23	O	H	S	H	HCl 290 (decomposition)
24	O	H	O	$-CH_3$	HCl 212—215 (decomposition)
25	O	H	S		maleate 180—181 (decomposition)
26	S	H	O	$-CH_3$	HCl 183 (decomposition)

EXAMPLE 27.

A mixture of 6.6 g. of 11 - [3 - (4-oxopiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin, 2.6 g. of potassium cyanide and 4.8 g. of piperidine hydrochloride in 10 ml. of water plus 40 ml. of ethanol is heated at 70°C. with stirring for 24 hours. After cooling, the solvent is distilled off under reduced pressure, and the residue is dissolved in 100 ml. of toluene and washed with water. The toluene layer is dried over anhydrous magnesium sulfate, and then the toluene is distilled off. The jelly-like residue (crude 11-[3 - (4 - cyano - 4 - piperidinopiperidino)-propylidene] - 6,11 - dihydrodibenz[b,e]-oxepin, 7.2 g.) thus obtained is dissolved in 50 ml. of 85% sulfuric acid under heating. The solution is heated at 75° to 95°C. for an hour. After cooling, the solution is added to 200 g. of ice and neutralized with an aqueous solution of sodium hydroxide. The oil liberated is extracted with toluene, the toluene layer is washed with water, dried and the toluene is distilled off. The residue is dissolved in ethanol, and hydrogen chloride gas is introduced into the solution. The crystals precipitated are collected and refined from aqueous ethanol to give 3.7 g. of 11 - [3-(4 - carbamoyl - 4 - piperidinopiperidino)-propylidene] - 6,11 - dihydrodibenz[b,e]-oxepin dihydrochloride 1/2 hydrate, melting at 283°C. (decomposition).

Proceeding by the method of Example 27, but substituting equivalent amounts of appro-

priate starting materials (IV), (V) and (VI), compounds (I), which are identical to the products of above Examples 1 and 3—11, are also produced.

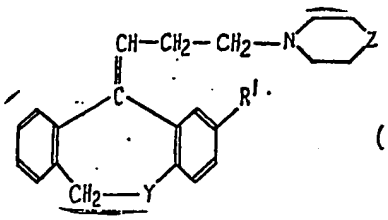
EXAMPLE 28.

A solution of 16 g. of 11 - [3 - (4 - oxopiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin in 50 ml. of tetrahydrofuran is added at 10° to 20°C. to a solution of phenyl magnesium bromide in tetrahydrofuran, which was prepared from 10.5 g. of phenyl bromide and 1.6 g. of metallic magnesium in 50 ml. of tetrahydrofuran. The resulting mixture is stirred at room temperature and then heated under reflux for 2.5 hours. After cooling, 100 ml. of a saturated ammonium chloride solution are added to the reaction mixture. The upper oil layer is extracted with toluene. The extract is washed with water, dried and concentrated. The remaining oil is dissolved in benzene, and 30 ml. of about 5% hydrochloric acid are added to the solution. The mixture is stirred to liberate a jelly-like hydrochloride. The benzene and water phases are removed by decantation and the jelly-like residue is dissolved in chloroform. After drying, the chloroform is distilled off, a small amount of acetone is added to the residue, and the whole is allowed to stand in a cold room. The crystals thus formed are collected and refined from aqueous acetone to give 12 g. of 11 - [3 - (4 - hydroxy - 4-phenylpiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin hydrochloride, melting at 212°—213°C.

Proceeding by the method of Example 28, but substituting equivalent amounts of appropriate starting materials (IV) and (VII), compounds (I), which are identical to the products of above Examples 2 and 12—18, are also produced.

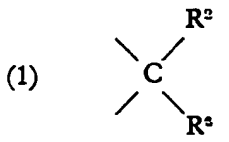
WHAT WE CLAIM IS:—

1. An N-substituted piperidine compound of the general formula:



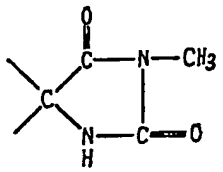
(I)

wherein Y is O, S or SO_2, R^1 is H, Cl, CH_3 or OCH_3 and Z is a bivalent group selected from groups of the formulae:



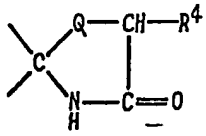
(1)

in which R^2 is OH, CN, $CONH_2$, COO_2H_5 or $COCH_3$ and R^3 is dimethylamino, piperidino, morpholino, phenyl, substituted phenyl (the substituent being Cl, CH_3 or CF_3) or acetylamino,



(2)

and



(3)

in which Q is O or S and R^4 is H, CH_3 or phenyl.

2. 11 - [3 - (4 - Carbamoyl) - 4 - piperidinopiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin.

3. 11 - [3 - (4 - Hydroxy - 4 - phenylpiperidino)propylidene] - 6,11 - dihydrodibenz[b,e])oxepin.

4. 2 - Chloro - 11 - [3 - (4 - carbamoyl-4 - piperidinopiperidino)propylidene] - 6,11-dihydrodibenz - [b,e]oxepin.

5. 11 - [3 - (4 - Hydroxy - 4 - *p* - chlorophenylpiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin.

6. 11 - [3 - (4 - Carbamoyl - 4 - morpholinopiperidino)propylidene] - 6,11 - dihydrodibenz[b,e]oxepin.

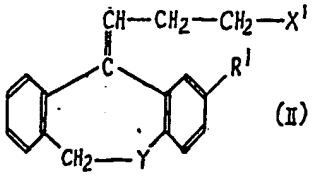
7. 11 - [3 - (2,4 - Dioxo - 3 - methyl-1,3,8 - triazaspiro[4.5]dec - 8 - yl)propylidene] - 6,11 - dihydrodibenz - [b,e]oxepin.

8. 11 - [3 - (1 - Thia - 3 - oxo - 4,8-diazaspiro[4.5]dec - 8 - ylpropylidene] - 6,11-dihydrodibenz[b,e] - oxepin.

9. A compound as claimed in Claim 1, substantially as hereinbefore described in the Examples.

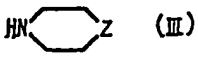
10. The pharmaceutically acceptable said addition salts of the compounds claimed in any preceding claim.

11. A method for producing a compound as claimed in Claim 1, which comprises reacting a compound of the general formula:



(II)

wherein Y and R^1 are as defined in Claim 1 and X^1 is a reactive radical, with a compound of the general formula:

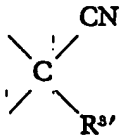


(III)

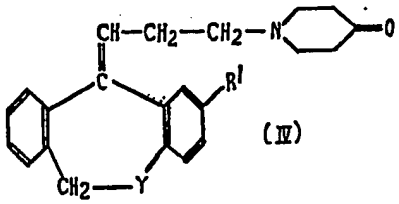
wherein Z is as defined in Claim 1, in a solvent at a temperature of 20° to 150°C. for a period of 5 to 10 hours.

12. A method as claimed in Claim 11, wherein the reactive radical is a halogen, methylsulfonyloxy, phenylsulfonyloxy or tolylsulfonyloxy radical.

13. A method for producing a compound as claimed in Claim 1 wherein Z is



($R^{3'}$ being dimethylamino, piperidino or morpholino), which comprises reacting a compound of the general formula:



(IV)

wherein Y and R^1 are as defined in Claim 1, with a cyanide of the formula:

$$Me \text{ —— } CN \qquad (V)$$

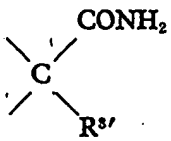
wherein Me is hydrogen or an alkali metal, and with an amine of the formula

$$H \text{ —— } R^{3'} \qquad (VI)$$

in an inert solvent at a temperature from 20°C. to the boiling point of the solvent employed for a period of 3 to 25 hours.

14. A method as claimed in Claim 13, wherein the reaction is carried out in water, an alcohol or a mixture thereof as the solvent.

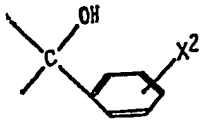
15. A method of producing a compound as claimed in Claim 1 wherein Z is



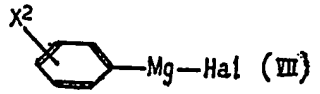
($R^{3'}$ being dimethylamino, piperidino or morpholino) which comprises hydrolyzing a compound prepared by the method defined in Claim 13 or 14.

16. A method as claimed in Claim 15, wherein the hydrolysis is carried out by the use of 5 to 20 moles of 70% to 95% by weight sulfuric acid per mole of the compound hydrolyzed, with heating at a temperature of 60° to 95°C. for a period of 30 minutes to 3 hours.

17. A method of producing a compound as claimed in Claim 1 wherein Z is



(X^2 being H, Cl, CH_3 or CF_3), which comprises reacting a compound of general formula (IV) as defined in Claim 13 with a Grignard reagent of the general formula:



(VII)

wherein Hal is halogen, and decomposing the reaction product with a dilute acid or aqueous ammonium chloride.

18. A method as claimed in Claim 17, wherein the reaction is carried out by mixing the compound of formula (IV) and compound of formula (VII) in an inert solvent, heating the resulting mixture at a temperature of 20°C. to the boiling point of the solvent employed for 2 to 30 hours, and finally decomposing the reaction product with a dilute acid or aqueous ammonium chloride solution.

19. A method of producing a compound as defined in Claim 1, substantially as hereinbefore described in any of the foregoing Examples.

20. An N-substituted piperidine compound of general formula (I), when produced by a method as claimed in any of Claims 11 to 19.

21. A pharmaceutical composition comprising a compound as claimed in any of Claims 1 to 10 or 20 and a pharmaceutically acceptable carrier therefor.

22. A composition as claimed in Claim 21, substantially as hereinbefore described.

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